

# PATENT COOPERATION TREATY

**PCT**

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
US Department of Commerce  
United States Patent and Trademark  
Office, PCT  
2011 South Clark Place Room  
CP2/5C24  
Arlington, VA 22202  
ETATS-UNIS D'AMERIQUE  
in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 21 March 2001 (21.03.01)	
<b>International application No.</b> PCT/US00/14122	<b>Applicant's or agent's file reference</b> NEB-163-PCT
<b>International filing date (day/month/year)</b> 23 May 2000 (23.05.00)	<b>Priority date (day/month/year)</b> 24 May 1999 (24.05.99)
<b>Applicant</b> XU, Ming-Qun et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
17 November 2000 (17.11.00)

☐ in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p style="text-align: center;"><b>The International Bureau of WIPO</b>                  34, chemin des Colombettes                  1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer</p> <p style="text-align: center; font-weight: bold;">Claudio Borton</p> <p>Telephone No.: (41-22) 338.83.38</p>
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## PCT

REC'D 08 OCT 2001

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

PCT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference NEB-163-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/14122	International filing date (day/month/year) 23 MAY 2000	Priority date (day/month/year) 24 MAY 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): C12N 15/10, 15/62, 15/64; C12P 21/02 and US Cl.: 435/69.1, 91.42; 536/23.4		
Applicant NEW ENGLAND BIOLABS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  17 NOVEMBER 2000	Date of completion of this report  23 AUGUST 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  TERRY A. MCKELVEY
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

**f. Basis of the report****1. With regard to the elements of the international application:\***☐ the international application as originally filed☒ the description:

pages (See Attached) \_\_\_\_\_, as originally filed

pages \_\_\_\_\_, filed with the demand

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_

☒ the claims:

pages (See Attached) \_\_\_\_\_, as originally filed

pages \_\_\_\_\_, as amended (together with any statement) under Article 19

pages \_\_\_\_\_, filed with the demand

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_

☒ the drawings:

pages (See Attached) \_\_\_\_\_, as originally filed

pages \_\_\_\_\_, filed with the demand

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_

☒ the sequence listing part of the description:

pages (See Attached) \_\_\_\_\_, as originally filed

pages \_\_\_\_\_, filed with the demand

pages \_\_\_\_\_, filed with the letter of \_\_\_\_\_

**2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.**

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).**3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:**☒ contained in the international application in printed form.☒ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.**4. ☒ The amendments have resulted in the cancellation of:**☒ the description, pages NONE☒ the claims, Nos. NONE☒ the drawings, sheets/fig. NONE**5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\***

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\*Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. statement**

Novelty (N)	Claims	<u>9-11, 14-15, 17-20, and 22-32</u>	YES
	Claims	<u>1-8, 12-13, 16, and 21</u>	NO
Inventive Step (IS)	Claims	<u>9-11, 14-15, 17-20, and 22-32</u>	YES
	Claims	<u>1-8, 12-13, 16, and 21</u>	NO
Industrial Applicability (IA)	Claims	<u>1-32</u>	YES
	Claims	<u>NONE</u>	NO

**2. citations and explanations (Rule 70.7)**

Claims 1-8, 12-13, 16, and 21 lack novelty under PCT Article 33(2) as being anticipated by Comb et al.

Comb et al teach splitting DNA coding for a target protein into fragments encoding the protein and inserting a DNA encoding a fragment of a controllable intervening protein sequence onto each terminus (C-terminus to N-terminus as appropriate for the target protein to be reconstituted by intein-mediated trans-splicing), thereby separating the DNA fragments so that the target protein is expressed in two fragments, each fragment comprising a part of a controllable intervening protein sequence. The target protein is then reconstituted from the expressed fragments (columns 16-18). Although this reference does not specifically teach that the purpose of the splitting of the DNA coding for the target protein followed by separating the DNA fragments is to prevent transmission to other organisms of the gene coding for the target protein, the steps that comprise the claimed method are all taught and thus the method taught by the reference would inherently result in preventing transmission as claimed. This reference teaches that the organism that the protein is expressed in can be *E. coli* (columns 16-17). The DNA molecule that the DNA fragments can be inserted into are taught as being any of DNA from a virus, plasmid, etc (columns 15-16).

Claims 9-11, 14-15, 17-20, and 22-32 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest compartmentizing each DNA fragment into separate specified cell compartments, use of protein complementation for reconstitution, analyzing the primary amino acid sequence of the target protein by specific methods in order to determine a potential split site, or specific isolated DNA fragments.

Claims 1-32 meet the criteria set out in PCT Article 33(4), for industrial applicability.

----- NEW CITATIONS -----

NONE

**Supplemental Box**

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

**I. BASIS OF REPORT:**

This report has been drawn on the basis of the description,  
page(s) 1-72 and 74-93, as originally filed.  
page(s) 73, filed with the demand.  
and additional amendments:  
NONE

This report has been drawn on the basis of the claims,  
page(s) 94-99, as originally filed.  
page(s) NONE, as amended under Article 19.  
page(s) NONE, filed with the demand.  
and additional amendments:  
NONE

This report has been drawn on the basis of the drawings,  
page(s) 1-33, as originally filed.  
page(s) NONE, filed with the demand.  
and additional amendments:  
NONE

This report has been drawn on the basis of the sequence listing part of the description:  
page(s) 1-41, as originally filed.  
pages(s) NONE, filed with the demand.  
and additional amendments:  
NONE

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/14122

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C12N 15/10, 15/62, 15/64; C12P 21/02

US CL : 435/69.1, 91.42; 536/23.4

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/69.1, 91.42; 536/23.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,834,247 A (COMB et al) 10 November 1998 (10.11.98), columns 2-3, 8-19.	1-6, 12-13, 16, 21
A	CHONG et al. "Single-column purification of free recombinant proteins using a self-cleavable affinity tag derived from a protein splicing element," Gene. 1997. Vol. 192, pages 271-281, see entire document.	1-32
A	XU. M-Q. "The IMPACT of Protein Splicing Research," The NEB Transcript. January 1997. Vol. 8, No. 2, pages 1-5, see entire document.	1-32

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

07 AUGUST 2000

Date of mailing of the international search report

07 SEP 2000

Name and mailing address of the ISA/US  
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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/14122

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>SOUTHWORTH et al. "Control of protein splicing by intein fragment reassembly," The EMBO Journal. 1998. Vol. 17, No. 4, pages 918-926, see entire document.</p>	1-32

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/14122

### B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

West (US and European databases), Dialog OneSearch (biotech databases)

search terms: intein, inteins, extein, exteins, als, acetolactate, epsps, enolpyruvyl, separat?, split?, protein splic?, affinity, compartment? complement?, linker?, loop?